REMARKS

A. Regarding the Amendments

Claim 1 has been amended as set forth in the attached "Version With Markings To Show Changes Made." As amended, the claims are supported by the specification and the original claims. Support for the amendment to claim 1, specifying that the *Renilla* luciferase of the invention has a recognition site at residues 197-200 of SEQ ID NO: 2 can be found, for example, on page 16, lines 13-15. Thus, upon entry of the amendments, claims 1, 3 and 5 to 8 will be pending.

B. Rejection Under 35 U.S.C. § 112

Applicant respectfully traverses the rejection of claims 1, 3 and 6 to 8 under 35 U.S.C. § 112, first paragraph, for containing subject matter allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the invention at the time of filing of the Application. In particular, it is alleged in Paper No. 21 that claims 1, 3 and 6 to 8 are directed to a genus of polypeptides of unlimited structure described by the function of having a decrease in protease activity upon cleavage by a protease. (Paper No. 21, page 5.) Applicant respectfully disagrees.

It is respectfully submitted that the application provides an adequate written description of not just the luciferase of SEQ ID NO: 2 substituted with a recognition site at residues 197-200, but for variants of SEQ ID NO: 2 with one or more recognition sequences. However, in the interest of advancing prosecution, claim 1 has been amended to add the language "and wherein the recognition site is at residues 197-200 of SEQ ID NO: 2." This language is supported in the specification, for example, at page 8, lines 23-27, page 16, lines 13-15 and originally filed claim 4. It is therefore respectfully submitted that the application provides an adequate written description of the luciferase of SEQ ID NO: 2 with a recognition site at residues 197-200. As amended, claim 1 sets forth both the structural and functional characteristics of the purified

polypeptide of the invention. Accordingly, the claims are not drawn to "a genus of polypeptides of unlimited structure," as alleged in Paper No. 21. Therefore, claims 1, 3 and 6-8 meet the written description requirement of 35 U.S.C. §112, first paragraph. Accordingly, removal of the rejection is requested.

Applicant respectfully traverses the rejection of claims 1, 3 and 6 to 8 under 35 U.S.C. § 112, first paragraph, for allegedly being non-enabled for luciferases different from SEQ ID NO: 2. In particular, it is alleged in Paper No. 21 that claims 1, 3 and 6 to 8 are directed to any luciferase different from SEQ ID NO: 2.

Initially, it is noted that the claims are not directed to all luciferases different from SEQ ID NO: 2. Claim 1 prior to the amendments included in the present response, was directed to a purified polypeptide with *Renilla* luciferase activity and a recognition site specifically protease-cleavable. However, in the interest of advancing prosecution, claim 1 has been amended to include the language "and wherein the recognition site is at residues 197-200 of SEQ ID NO: 2." This language is supported in the specification, for example, at age 8, lines 23-27, page 16, lines 13-15 and originally filed claim 4. It is respectfully submitted that one of skill in the art would have known, at the time of filing of the present invention, how to substitute the sequence of SEQ ID NO: 2 with one or more protease-cleavable recognition sites at residues 197-200 to obtain a polypeptide with *Renilla* luciferase activity, wherein cleavage by a protease results in a decrease in luciferase activity and wherein the recognition site is at residues 197-200 of SEQ ID NO: 2.

As such, one of skill in the art would have been able to practice the present invention, as the amended claims specify a purified polypeptide with *Renilla* luciferase activity and a recognition site at residues 197-200 specifically cleavable by protease, wherein cleavage results in a decrease in luciferase activity and wherein the recognition site is at residues 197-200 of SEQ ID NO: 2. Therefore, claims 1, 3 and 6 to 8 meet the enablement requirement of 35 U.S.C. §112, first paragraph. Accordingly, the removal of the rejection is requested.

C. **Rejection Under 35 U.S.C. § 102**

Applicant respectfully traverses the rejection of claim 1 to 3 and 6 to 8 under 35 U.S.C. 102(b) as allegedly anticipated by Korant et al.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (In re Spada, 15 USPQ 2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 2d 1566 (Fed. Cir., 1990). It is respectfully submitted that the reference of Korant does not teach all of the elements of the claimed invention. Claim 1 claims a purified polypeptide with *Renilla* luciferase activity and a recognition site specifically cleavable by a protease, wherein cleavage results in a decrease in luciferase activity and wherein the recognition site is at residues 197-200. Korant does not teach the specific sequence of SEQ ID NO: 2, nor does it teach modification of that sequence to obtain a variant of *Renilla* luciferase. In fact, Korant teaches away from the modification of the *Renilla* luciferase, as Korant remarks that cleavage of non-viral proteins is rarely observed with HIV-1 protease, but that *Renilla* luciferase was cleaved by the protease. As a cleavable non-viral protein was found in *Renilla* luciferase for purposes of the assay, no further modification was taught. While Korant teaches the cleavage of *Renilla* luciferase by various proteases, it also shows that by comparison, other proteases were not very successful in the degradation of luciferase, such as thromin and fXa. No suggestion was made to modify the luciferase to contain a binding site of any of these proteases to increase the degradation of luciferase. As Korant does not teach all of the elements of the claimed invention, it is respectfully submitted that claim 1 and the claims dependent therefrom are not anticipated by Korant.

D. **Rejection Under 35 U.S.C. § 103**

Applicant respectfully traverses the rejection of claims 1 to 3 and 6 to 8 under 35 U.S.C. 103(a) as allegedly unpatentable over Lorenz et al, in view of Xu et al. In order for an invention to be obvious, the differences between the subject matter of the application and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art. In order to meet this standard, the combination of references must teach or suggest all of the elements of the claimed invention. It is respectfully submitted that Lorenz et al, in view of Xu et al does not teach or suggest all of the elements of the claimed invention.

It is alleged in Paper No. 21 that the combined teachings of Lorez and Xu would have made it obvious to one of skill in the art to make a *Renilla* luciferase substituted with the DEVD recognition site of caspase-3. Applicant respectfully disagrees and submits that the Lorenz reference, in view of Xu, does not teach or suggest the claimed invention

The Lorenz reference teaches that *Renilla* luciferases may be used as a marker in mammalian cells. Lorenz does not teach or suggest an isolated polypeptide with *Renilla* luciferase activity and a recognition site specifically cleavable by a protease, and with a recognition site at residues 197-200 of SEQ ID NO: 2. The Xu reference does not teach the omissions of the Lorenz reference.

As previously stated, the Xu reference discusses a green fluorescent protein (GFP) linked to a blue fluorescent protein (BFP) via an 18 amino acid region containing a DEVD sequence. The paper examines the effect on the fluorescence energy transfer (FRET) between the GFP and the BFP in the presence of caspase-3 and through the subsequent cleavage of the GFP-BFP complex. The Examiner has asserted in Paper No. 21 that one of ordinary skill in the art would have had motivation to use other luminescent protein markers in monitoring the presence of caspase-3. However, the mechanisms of Xu and the claimed invention are different, such that the combination of the Xu and Lorenz references do not teach or suggest all of the elements of the claimed invention.

The Xu reference teaches that a decrease in FRET between the GFP and the BFP linked with DEVD indicates the presence of caspase-3. The decrease measured is the interaction

between the GFP and the BFP. The Xu reference does not teach or suggest insertion of the DEVD sequence within either of the fluorescence proteins, such that cleavage would be cleavage of a protein itself and subsequent decrease in fluorescence of the protein. The Xu reference does not teach that a decrease in GFP fluorescence or BFP fluorescence alone would indicate the presence of caspase-3. In the present invention, the cleavage of the isolated polypeptide with *Renilla* luciferase activity results in diminished luciferase activity, though still detectable, as compared with wild type *Renilla* luciferase. As such, the Xu reference does not teach or suggest the elements of the claimed invention not taught in the Lorenz reference. The Xu reference fails to teach or suggest that cleavage by a protease results in a decrease in activity of a fluorescence protein individually.

It is respectfully submitted that the Lorenz reference, alone or in combination with the Xu reference, does not teach or suggest all of the elements of the claimed invention. Neither reference alone or in combination with the other reference teaches or suggests that a purified polypeptide with *Renilla* luciferase activity of SEQ ID NO: 2 may be modified to contain a recognition site specifically cleavable by a protease, wherein the cleavage results in a decrease in luciferase activity. Therefore, it is respectfully submitted that the Lorenz reference, in view of the Xu reference does not render independent claim 1, or the claims dependent therefrom, obvious under 35 USC 103(a). Accordingly, removal of the rejection is requested.

Applicant respectfully traverses the rejection of claims 1 to 3 and 6 to 8 under 35 U.S.C. 103(a) as allegedly unpatentable over Korant et al, in view of Xu et al. It is respectfully submitted that Korant et al, in view of Xu et al does not teach or suggest all of the elements of the claimed invention, as would be required to show the claimed invention as obvious.

The Examiner has stated that "[t]he difference between the reference of Korant et al. and the instant invention is that the reference of Korant et al. does not teach a luciferase having the recognition and cleavage site of caspase-3." While Applicant agrees that Korant does not teach the protease caspase-3, Applicant also asserts, as set forth above, that Korant does not teach or

suggest use of a variant of *Renilla* luciferase in the assay for HIV-1 protease activity. It is respectfully set forth that the claimed invention claims a purified polypeptide that has *Renilla* luciferase activity and a recognition site specifically cleavable by a protease, and wherein the recognition site is at residues 197-200 of SEQ ID NO: 2. It is also respectfully submitted that Xu does not remedy the omissions of Korant. As set forth above, Xu teaches that the recognition and cleavage site of caspase-3 is DEVD, but does not teach or suggest insertion of that site into a protein. However, as set forth above, Korant does not teach or suggest modifying the *Renilla* luciferase of the disclosed assay and therefore one of skill in the art would not be motivated to combine these references.

Therefore, it is respectfully submitted that Korant, in view of Xu does not render claims 1, 3 or 6 to 8 or the claims dependent therefrom, obvious under 35 USC 103(a). Accordingly, removal of the rejection is requested.

CONCLUSION

In summary, for the reasons set forth herein, Applicant maintains that claims 1 and 3 to 8 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 1 has been amended as follows:

1. (Twice amended) A purified polypeptide characterized as having *Renilla* luciferase activity and a recognition site specifically cleavable by a protease, wherein cleavage results in a decrease in luciferase activity and wherein the recognition site is at residues 197-200 of SEQ ID NO: 2.